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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,805	04/08/2005	Richard L Guerrant	00826-03	9328

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UNIVERSITY OF VIRGINIA PATENT FOUNDATION
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EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,805	GUERRANT ET AL.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *8,18 and 23-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9-17, 19-22* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Election/Restriction filed on June 22, 2007 is acknowledged. Claims 1-30 are pending in this application.

Restriction

1. Applicant's election of Group I (claims 1-23, 25 and 26) drawn to a product: a composition comprising a glutamine-bearing compound; and a first method: a method of enhancing the absorption of a pharmaceutical agent administered orally to a mammal and the election of species $ALA(GLN)_n$ for the amino acid sequence, nelfinavir for the antiretroviral drug, and trypsin for the protease cleavage site in the reply filed on June 22, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 24-30 are withdrawn from further consideration, pursuant to 37 CFR 1.142(b), as being drawn to nonelected invention, there being no allowable generic or linking claims. Claims 8, 18 and 23 are withdrawn from further consideration as being drawn to a nonelected species. Claims 1-7, 9-17 and 19-22 are examined on the merits in this office action.

Objection-Minor Informalities

3. The title is objected to because the title is too long. The title is limited to 2-7 words maximum. A new title is required that is clearly indicative of the invention to which

the claims are directed. The following title is suggested: "Stable Glutamine Derivatives to Improve Drug Absorption".

Rejection-35 U.S.C. 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 3-7, 9-11, 13-17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Guerrant et al (US Patent # 5561111).

6. The instant claims are drawn to a method of enhancing the absorption of a pharmaceutical agent administered orally to a mammal, the method comprising the steps of administering to the mammal a composition comprising a glutamine-bearing compound ($Ala(Gln)_n$), and administering orally to the mammal the pharmaceutical agent, wherein the mammal is a human subject having compromised intestinal function.

7. Guerrant et al teach a method for the treatment of dehydration or nitrogen deficiency-based malnutrition involving administering to a patient in need thereof an effective amount of a compound selected from oligopeptides formed from the coupling of one or more amino acid with glutamine, the product of coupling glucose with glutamine, the product of coupling glucose and one or more amino acids with glutamine, or the product from acylating glutamine with a carboxylic acid having from 2 to 6 carbon

atoms (see abstract). This reads on claims 1, 3-5, 11 and 13-15, since glucose can be used as a pharmaceutical agent as a restorative agent after severe operation or as a nutritive in wasting diseases, as evidenced by the British Pharmaceutical Codex (see www.henriettesherbal.com/eclectic/bpc1911/glucosum.html). Furthermore, the reference teaches that glutamine derivatives effectively block the degradation of glutamine in the highly acidic conditions, which are encountered in the human stomach. In order to perform effectively in oral therapy, the compounds must be able to survive the conditions in the digestive tract while maintaining the ability to stimulate their absorption and maintain the integrity of the intestinal mucosa (see column 4, lines 12-18). Furthermore, the reference teaches that the glutamine derivatives can be administered either orally or intravenously (see column 4, lines 24-25). This reads on claim 4. Additionally, the reference teaches that the glutamine-bearing compound is Ala-Gln (see Example and Figure 1). This reads on claims 6, 7, 9-10, 16-17 and 19. Thus, the prior reads on claims 1, 3-7, 9-11, 13-17 and 19.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1, 11 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Petit et al (US Patent # 6734170).

9. The instant claims are drawn to a method of enhancing the absorption of a pharmaceutical agent administered orally to a mammal, the method comprising the

steps of administering to the mammal a composition comprising a glutamine-bearing compound, and administering orally to the mammal the pharmaceutical agent, wherein the mammal is a human subject who is HIV positive, having compromised intestinal function and the administered pharmaceutical agent is an antiretroviral drug.

10. Petit et al teach a composition and a method for increasing cellular uptake of bioactive agents, particularly those compounds termed "small molecules" into the cells of mammalian tissue, such as the epithelial cells of the mucosa (see abstract). The reference teaches that the composition is a solution dispersion or suspension comprising an aqueous vehicle and an effective amount of a bioactive compound, in combination with an amount of carbohydrate effective to reduce the absolute solubility of the bioactive agent in the aqueous vehicle, so as to achieve increased transport (absorption) of the bioactive agent into the target cells (see column 2, lines 35-41). The reference teaches that administration of the composition can provide treatment for a variety of physiologic disorders ameliorated by enhancement of absorption of bioactive agents into damaged or intact tissues (see column 3, lines 5-8). This reads on claim 1 in part. The reference teaches that the term "bioactive agent" refers to a molecule that exerts a therapeutic or nutritive effect on a mammal following absorption of an effective amount of the molecule by the target (see column 4, lines 9-12). the small molecules that may be potentiated include antiviral drugs and antibiotics (see column 4, lines 55-56) and the specific antiviral agents include acyclovir, acyclovir sodium, amantadine...zidovudine (AZT or ZDY), HPA-23, abacavir (Ziagen®) (see column 5, lines 4-7). This reads on claim 12 in part. The reference further teaches "enhancement

of glutamine absorption to treat patients infected with HIV" in column 18. The reference teaches that enhancing glutamine absorption into the intestinal mucosa by the method of administering the composition can provide a therapeutic benefit to HIV-infected patients, particularly those patients who are in the early stages of infection. Enhancement of the cytokine response to the viral infection can contribute to viral destruction by the immune system at the site of significant viral replication (see column 18, lines 30-36). Furthermore, the glutamine/carbohydrate carrier composition can be administered in the form of an enteric-coated tablet, caplet, capsule, or coated bead (see column 18, lines 37-39). This reads on claims 1, 11 and 12.

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1, 11 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Petit et al (US Patent # 6734170).

12. The instant claims are drawn to a method of enhancing the absorption of a pharmaceutical agent administered orally to a mammal, the method comprising the steps of administering to the mammal a composition comprising a glutamine-bearing compound, and administering orally to the mammal the pharmaceutical agent, wherein the mammal is a human subject who is HIV positive, having compromised intestinal function and the administered pharmaceutical agent is an antiretroviral drug.

13. Petit et al teach a composition and a method for increasing cellular uptake of bioactive agents, particularly those compounds termed "small molecules" into the cells of mammalian tissue, such as the epithelial cells of the mucosa, as described supra.

Rejection-35 U.S.C. 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 2, 12 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guerrant et al (US Patent # 5561111) as applied to claims 1, 3-7, 9-11, 13-17 and 19 above, and further in view of Petit et al (US Patent # 6734170).

18. The instant claim is drawn to a method of enhancing the absorption of a pharmaceutical agent administered orally to a mammal, the method comprising the steps of administering to the mammal a composition comprising a glutamine-bearing compound administered prior to the administration of the pharmaceutical agent, and administering orally to the mammal the pharmaceutical agent, wherein the mammal is a human subject who is HIV positive, having compromised intestinal function and the administered pharmaceutical agent is an antiretroviral drug, zidovudine.

19. Guerrant et al teachings are described supra. The difference between the reference and the instant claim is that the reference does not teach a human subject who are HIV positive and the administration of a pharmaceutical agent that is an antiretroviral drug.

20. However, Petit et al teach a composition and a method for increasing cellular uptake of bioactive agents, particularly those compounds termed "small molecules" into the cells of mammalian tissue, such as the epithelial cells of the mucosa (see abstract). The reference teaches that the composition is a solution dispersion or suspension comprising an aqueous vehicle and an effective amount of a bioactive compound, in combination with an amount of carbohydrate effective to reduce the absolute solubility of the bioactive agent in the aqueous vehicle, so as to achieve increased transport (absorption) of the bioactive agent into the target cells (see column 2, lines 35-41). The reference teaches that administration of the composition can provide treatment for a variety of physiologic disorders ameliorated by enhancement of absorption of bioactive agents into damaged or intact tissues (see column 3, lines 5-8). The reference teaches

that the term "bioactive agent" refers to a molecule that exerts a therapeutic or nutritive effect on a mammal following absorption of an effective amount of the molecule by the target (see column 4, lines 9-12). the small molecules that may be potentiated include antiviral drugs and antibiotics (see column 4, lines 55-56) and the specific antiviral agents include acyclovir, acyclovir sodium, amantadine...zidovudine (AZT or ZDY), HPA-23, abacavir (Ziagen®) (see column 5, lines 4-7). The reference further teaches "enhancement of glutamine absorption to treat patients infected with HIV" in column 18. The reference teaches that enhancing glutamine absorption into the intestinal mucosa by the method of administering the composition can provide a therapeutic benefit to HIV-infected patients, particularly those patients who are in the early stages of infection. Enhancement of the cytokine response to the viral infection can contribute to viral destruction by the immune system at the site of significant viral replication (see column 18, lines 30-36). Furthermore, the glutamine/carbohydrate carrier composition can be administered in the form of an enteric-coated tablet, caplet, capsule, or coated bead (see column 18, lines 37-39). Additionally, the reference teaches that in any of these preparations, glutamine has a stable shelf-life and can be provided to the patient well in advance of the time of administration. The preparations can be stored in the clinic or the patient's home for administration as needed (see column 20, lines 40-44).

21. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Guerrant et al and Petit et al, since both prior arts teach a carbohydrate-Glutamine composition that enhances cellular uptake of bioactive agents into the cells of mammalian tissues (see Patent '111, column 4, lines 12-18 and Patent

'170, column 2, lines 31-34). One of ordinary skill in the art would be motivated to combine the teachings since glutamine supplementation has been shown to provide numerous benefits, including stimulation of certain cells of the immune system (see Patent '170, column 1, lines 51-53) and glutamine/carbohydrate can provide a therapeutic benefit to HIV-infected patients (see Patent '170, column 18, lines 30-32). There is a reasonable expectation of success since Petit et al teach that glutamine/carbohydrate carrier composition can be used to treat HIV and further teach specific antiviral agents such as zidovudine (AZT) that may be potentiated into the composition (see column 4, lines 55-58 and column 5, line 7).

22. The MPEP states the following: *"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art."* In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and Ex parte Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). But see In re Geiger, 815

F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive....Appellant argues... hindsight reconstruction or at best,... obvious to try'.... We agree with appellant."). Since Petit et al teach glutamine/carbohydrate composition can be used to treat HIV and it is well known in the art that AZT is an antiretroviral agent utilized in the treatment of HIV, it would be obvious to combine an antiretroviral agent with glutamine/carbohydrate to treat the same disease, since the third compound would at least have an additive effect.

Conclusion

23. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Julie Ha
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7/18/07
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